REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

At the outset, the undersigned wishes to express sincere appreciation to the Examiner and her supervisor for the very constructive interview of August 10, 2007. While the Examiner's Summary reflects the substance of the interview, the undersigned points out that the Examiner acknowledged during the interview that the inclusion of claim 79 (which makes no reference to "a polymer") in the rejection under 35 USC 103 over Wagner, in light of the Merck Index, in view of Wainwright et al and Shanbrom was an error (see comments that follow responsive to that rejection).[1]

As indicated in the Examiner's Summary, the activity of certain compounds described in Table 5 was discussed during the interview and the Examiner and her supervisor expressed the view that claims limited to such compounds would have been unobvious and would be enabled. In order to advance prosecution of this application, the claims have been amended so as to recite Compounds Nos. 1-3, 7, 8, 10-15, 18, 20 and 21 from Table 5 (support for the revision can be found to page 6, line 27 to page 7, line 13). That the claims have been so limited should not be taken as an indication that Applicants agree with any view expressed by the Examiner in the Office Action. Rather, as indicated above, the revisions have been made merely to advance prosecution of this application and Applicants reserve the right to pursue any deleted subject matter in a continuation application.

[1] The Examiner Summary of the telephonic interview of July 13, 2007 also adequately reflects the substance of that interview and thus no further comment is believed to be necessary. It is requested that this statement be treated as a "Statement of the Substance of the Interview".

For the Examiner's ease of reference, the cations of the compounds recited in the claims as now presented are listed below, together with the relevant microbial "Cell Kill (log_{10} reduction in CFU/ml)" data from column 7 of Table 5:

Cation		Cell Kill (log_{10} reduction in CFU/ml)
3,7-(tetra-n-propylamino)-phenothiazin-5-ium	("**Propylene Blue**")	0.91 (0.12)
3,7-(tetra-n-butylamino)-phenothiazin-5-ium	("**Butylene Blue**")	4.72 (0.30)
3,7-(tetra-n-pentylamino)-phenothiazin-5-ium	("**Pentylene Blue**")	5.29 (0.25)
3,7-(tetra-iso-pentylamino)-phenothiazin-5-ium		3.58 (0.13)
3-(N,N-di-n-butylamino)-7-(N,N-di-n-propylamino)-phenothiazin-5-ium		4.86 (0.30)
3-(N,N-di-n-hexylamino)-7-(N,N-di-n-propylamino)-phenothiazin-5-ium		4.62 (0.34)
3-(2-ethylpiperidino)-7-(N,N-di-n-pentylamino)-phenothiazin-5-ium		3.56 (0.27)
3-(2-methylpyrrolidino)-7-(N,N-di-n-pentylamino)-phenothiazin-5-ium		3.21 (0.07)
3,7-(N,N-tetra- iso-butylamino)-phenothiazin-5-ium		2.56 (0.09)
3-(N,N-di-n-butylamino)-7-(N,N-di-iso-pentylamino)-phenothiazin-5-ium		2.84 (0.30)
3-(N,N-diethylamino)-7-(N,N-di-n-propylamino)-phenothiazin-5-ium		3.01 (0.14)
3-(N,N-di-n-pentylamino)-7-(N,N-di-n-propylamino)-phenothiazin-5-ium		4.50 (0.28)
3-(N,N-di-n-butylamino)-7-(N,N-di-n-pentylamino)-phenothiazin-5-ium		3.25 (0.58)
3-((N-ethyl-N-cyclohexyl) amino)-7((-N–ethyl)-N-cyclohexyl) amino-phenothiazin-5-ium		4.74 (0.10)

It will be clear from a review of the foregoing that the photo-inactivation (microbial cell kill) observed using the compounds of Table 5 listed above, and recited in the claims as now presented, is substantially higher than that of the tetramethyamino phenothiazinium ("Methylene Blue" - compound 5 in Table 5) (0.55 (0.02)) and tetraethylamino phenothiazinium ("Ethylene Blue" – compound 6 in Table 5) (0.23 (0.02)) compounds which were specifically excluded from the claims as previously presented. As pointed out to the Examiner at the time of the interview, this increase in photo-antimicrobial activity was *wholly* unexpected because the perception in the art at the relevant date was that any decrease in water solubility would result in a decrease, rather than an increase, in such activity (note, particularly, the significantly lower photo-antimicrobial activity observed when taking the first step up to a higher homologue (i.e., from

Methylene Blue to Ethylene Blue)). Details of this perception, and the basis therefor, are set forth in the Declaration by Dr. David Lewis submitted herewith[2]. As pointed out on page 7 of the Lewis Declaration, the approximate water solubility at 25° C is 5g/100ml for Methylene Blue, 3.9 g/100 ml for Ethylene Blue and only 0.01g/100ml for "Propylene Blue", 0.015g/100ml for "Butylene Blue" and 0.0001g/100ml for "Pentylene Blue" ("Propylene Blue", "Butylene Blue" and "Pentylene Blue" being the first 3 compounds listed above and in the claims). Thus, despite the fact that Ethylene Blue is approximately 390 times more soluble in water than "Propylene Blue", it has substantially lower photo-antimicrobial activity (0.23 (0.02) for Ethylene Blue versus 0.91 (0.12) for "Propylene Blue").

Prior to turning to the rejections set forth in the Office Action, the Examiner's attention is directed to the fact that, in addition to the revision of independent claims 77, 79, 84 and 100 to recite specific compounds from Table 5, claim 78 has been revised so as to be consistent with the format used in claim 77 from which it depends, and new dependent claims 101-103 have been added. The new claims find support as follows:

101 - page 5, lines 4-8,

102 - page 7, lines 13 and 14.

103 - page 6, lines 30 and 31 and page 7, lines 12 and 13.

[2] The Declaration submitted herewith corresponds to the draft provided to the Examiner in advance of the interview except for the fact that the former includes a more accurate value for the solubility of Ethylene Blue than was available at the time of the interview and reference is made to the source of the solubility data.

RESPONSE TO REJECTIONS:

Claim 79 stands rejected under 35 USC 102 as allegedly being anticipated by Mazur. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of claim 79 and for the reasons that follow.

The phenothiazine compounds defined in Mazur are:

- those with a saccharide residue (Column 1, line 65) - such phenothiazinium compounds are not within the scope of the compounds recited in claim 79 as now presented; and
- those where R_1 and R_2 are both methyl and Y is a bond (i.e., a direct link between the N atom and the R_1 group) (column 2, line 3) - such compounds are among the list of compounds recited in claim 79 as now presented.

None of the compounds described generically or specifically in Mazur falls within the scope of the compounds in amended claim 79. Consequently, amended claim 79 is novel over Mazur. Withdrawal of the rejection is clearly in order and same is requested.

Claims 79 and 84 stand rejected under 35 USC 103 as allegedly being obvious over Wagner, in light of the Merck Index, in view of Wainwright et al and Shanbrom. Withdrawal of the rejection is submitted to be in order in view of the above-noted revision of claim 84 to recite specific compounds from Table 5 and further in view of the comments that follow.

Claim 79 does not make reference to "a polymer" and thus the inclusion of claim 79 in this rejection is an error. As pointed out above, the Examiner acknowledged such to be the case during the interview.

Wagner discloses a method for decontaminating blood and cellular components using certain phenothiazinium dyes and mentions at page 8 Methylene Blue, toluidine O, thionin, azure A, azure B and azure C. The Examiner relies on Wainwright et al for "its teaching of the

antibacterial properties of methylene blue against *S. aureus* and methicillin-resistant *S. aureus*" and on Shanbrom for its teaching of "an organic polymer material to which is tightly adsorbed a disinfectant organic dye …. such as methylene blue…".

While the Examiner appreciates that Applicants' invention does not include the use of Methylene Blue, the Examiner contends that:

> …the use of a compound homologous to methylene blue that solely differs in the length of the hydrocarbon chain (i.e., wherein the two methyl groups are substituted by, for example, two propyl groups, or two butyl groups, etc.) and, therefore, would share significant structural homology to methylene blue *per se*, would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention. Such a person would have been motivated to use such a compound(s) with a reasonable expectation of success in achieving the same, or substantially similar therapeutic benefit to the patient, because the shared structural similarities and, thus, homology between the compounds, would have reasonably predicted that the compounds would have shared similar pharmacological properties due to their homologous chemical structures.

As pointed out at the time of the interview, and as the Examiner and her supervisor appreciated, the compounds from Table 5 recited in the claims as now presented provide unexpectedly improved antimicrobial activity over Methylene Blue and thus their use in the method of the invention would not have been obvious over the cited art.

In the attached Declaration, Dr. Lewis explains that the conventional thinking in the relevant art at the time of the invention was that there was a relationship between the water solubility of cationic dyes and the effectiveness of such dyes as biological stains. Specifically, Dr. Lewis points out that convention would have taught that a significant decrease in the water solubility of a dye would be detrimental to its photo-antimicrobial activity. Accordingly, one skilled in the art would not have considered higher homologues of Methylene Blue as these show

a very rapid decrease in water solubility with increasing chain length. Furthermore, as Dr. Lewis goes on to explain, even if an artisan were to have considered higher homologues, he/she would have expected poorer results rather than the significantly improved results described above (and in Table 5 of the application) since Ethylene Blue has a significantly lower photo-antimicrobial activity than Methylene Blue. Thus, a researcher systematically investigating the effect of increased alkyl chain length on photodynamic activity would have found that extending the chain length from methyl to ethyl resulted in a decrease in activity and, thus, would have been further dissuaded from examining even longer chains (e.g., propyl, butyl, etc). The sudden increase in photo-antimicrobial activity from Ethylene Blue to Propylene Blue would have been unexpected on two counts: (a) the dramatically reduced water solubility of the latter relative to the former (~400 fold reduction), and (b) the reversal of the trend in activity from methyl to ethyl.

It will be clear from the above that Wagner would not have suggested that compounds recited in the present claims would be useful for sterilizing a surface or fluid, much less would Wagner have suggested the advantageous properties of the presently recited compounds. Combining Wagner with Wainwright et al would not have brought the skilled person any closer to the instant invention. Indeed, rather than increasing alkyl chain length of the hydrocarbon group on the N atom to improve activity, Wainwright et al teaches that ring substitution by two methyl groups improves activity. Shanbrom offers nothing that would have cured the fundamental failings of Wagner and Wainwright et al as Shanbrom merely teaches organic polymer materials to which a disinfectant dye is adsorbed.

Given the conventional wisdom in the relevant art (detailed in the Lewis declaration), the skilled person would not have found any motivation in the citations upon which the Examiner relies to endeavor to use the compounds recited in the claims to kill or deactivate

microorganisms present in a fluid in the manner required by Applicants' invention, much less would one have expected the use of such compounds to yield the photo-antimicrobial results described above and in Table 5. Accordingly, withdrawal of the rejection is requested.

Claims 77, 79, 89-91, 98 and 99 stand rejected under 35 USC 103 as allegedly being obvious over Wilson et al, in light of the Merck Index, in view of Biel and Wainwright et al. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and comments that follow.

At the outset, it is noted that the Examiner refers to Biel (WO 01/62289; 2001). As pointed out at the interview, Biel (WO 01/62289) is citable only as of its August 30, 2001 publication date as it does not designate the US. August 30, 2001, however, is after the earliest of the dates from which this case claims priority (May 30, 2001) (the priority claim has been perfected), thus, Biel (WO 01/62289) is not properly citable against the present application. That said, WO 01/62289 claims priority from US Appln. No. 09/792,578, filed February 23, 2001, which has published and thus is citable as of its filing date. From a preliminary review of Appln. No. 09/792,578, it appears to be the same as WO 01/62289. Accordingly, as pointed out to the Examiner at the interview, this rejection will be treated as though it was based on the published counterpart of Appln. No. 09/792,578.

In rejecting the claims as obvious over Wilson et al, Biel and Wainwright et al, the Examiner again states:

> …the use of a compound homologous to methylene blue that solely differs in the length of the hydrocarbon chain (i.e., wherein the two methyl groups are substituted by, for example, two propyl groups, or two butyl groups, etc.) and, therefore, would share significant structural homology to methylene blue *per se*, would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention. Such a person would have been

> motivated to use such a compound(s) with a reasonable expectation of success in achieving the same, or substantially similar therapeutic benefit to the patient, because the shared structural similarities and, thus, homology between the compounds, would have reasonably predicted that the compounds would have shared similar pharmacological properties due to their homologous chemical structures.

As pointed out at the interview and above, the compounds from Table 5 recited in the claims as now presented provide unexpectedly improved activity over Methylene Blue and thus their use in the method of the invention would not have been obvious over the cited art.

As discussed above, Dr. Lewis makes clear in his Declaration that the conventional thinking in the art would have taught that a decrease in dye water solubility would be detrimental to photo-antimicrobial activity. Accordingly, one skilled in the art would not have considered higher homologues of Methylene Blue because of their expected and actual lower water solubilities. Even if an artisan were to have considered higher homologues, he/she would have expected poorer results rather than the significantly improved results described above (and in Table 5 of the application). As Dr. Lewis points out, a researcher systematically investigating the effect of increased alkyl chain length on photo-antimicrobial activity would have found that extending the chain length from methyl to ethyl resulted in a decrease in activity and, thus, would have been dissuaded from examining even longer chains (e.g., propyl, butyl, etc).

Wilson discloses a method of disinfecting or sterilizing tissues in the oral cavity or a wound or lesion in the oral cavity. Wilson lists a random selection of dyes and other compounds at column 2 and in Table 1. As discussed above with reference to Wagner, none of these compounds fall within the scope of the compounds recited in the instant claims.

There is no general theme in Wilson that would have assisted a skilled person in understanding what structure activity relationships are taught. Wilson uses phenothiazine dyes that featured in Wagner and from these the skilled person would have reasonably concluded that phenothiazine compounds with amino or methylamino or dimethylamino groups attached to the ring would be appropriate. There is nothing in Wilson that would have suggested to the skilled person that increasing the alkyl chain length of the hydrocarbon group on the N atom would even be worth trying, much less is there anything that would have suggested that an increase in chain length would improve activity as Applicants have discovered quite unexpectedly. Indeed, based on the conventional wisdom in this art at the relevant date (see Lewis Declaration), a decrease in activity would have been expected.

Biel discloses a random set of dyes, particularly Methylene Blue, which, as discussed above, is not within the scope of the present invention.

Thus, both Wilson and Biel disclose methods employing dyes that are outside the scope of the compounds recited in present claims. Neither document, taken alone or in combination, teaches or would have suggested the use of the presently recited dyes in the sterilizing method of the instant invention, much less that the recited compounds would have the advantageous properties discussed above.

The teachings of Wainwright et al are discussed above. Briefly, this reference teaches structurally changing Methylene Blue by adding two methyl groups to the phenothiazine ring and that such ring substitution improves activity. Wainwright et al thus adds nothing to the combination of Wilson et al and Biel that would have brought one skilled in the art closer to the instant invention.

In view of the above, reconsideration is requested.

Claims 77, 79, 89-91 and 98 - 100 stand rejected under 35 USC 103 as allegedly being obvious over by Wilson et al, in view of Biel and Wainwright et al and further in view of Chowdhary et al. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and comments that follow.

The lack of citability of Biel (WO 01/62289) is discussed above - those comments are equally relevant here.

In rejecting the claims as obvious over Wilson et al, Biel, Wainwright et al, and Chowdhary et al the Examiner states that an artisan:

> … would have found it *prima facie* obvious to use the disclosed methylene blue compound of Wilson et al., or structurally homologous compounds (i.e., those with extended hydrocarbon chain substitutions as discussed *supra*) for the treatment of psoriatic lesions as disclosed by Chowdhary et al. with a reasonable expectation of success because Chowdhary et al. expressly discloses the amenability of such lesions to treatment via photodynamic therapy using phenothiazinium-based photosensitizing compounds, such as, e.g., methylene blue-type compounds, exposed to light. Furthermore, the reasonable expectation of similar pharmacologic properties of phenothiazinium compounds with extended hydrocarbon chain substitution (as compared with the methylene-blue type compounds disclosed by Chowdhary et al.) would also have suggested to one of ordinary skill in the art at the time of the invention that such compounds would also have exhibited similar efficacy in treating psoriatic lesions similar to that of methylene blue, absent factual evidence to the contrary.

Submitted herewith, in the form of the Lewis Declaration, is evidence that supports Applicants' position that the compounds from Table 5 recited in the claims as now presented provide unexpectedly improved activity over Methylene Blue and thus their use in the method of the invention would not have been obvious over the cited art.

As pointed out above, Dr. Lewis explains in his Declaration that the conventional wisdom in the relevant art would have taught that a significant decrease in dye water solubility would be detrimental to photodynamic therapy. Accordingly, one skilled in the art would not have considered higher homologues of Methylene Blue because of their expected and actual lower water solubilities. As discussed above, a researcher systematically investigating the effect of increased alkyl chain length on photo-dynamic activity would have found that extending the chain length from methyl to ethyl resulted in a decrease in activity and, thus, would have been dissuaded from examining even longer chains (e.g., propyl, butyl, etc).

The teachings of Wilson, Biel, and Wainwright et al are discussed above. Chowdhary et al relates to formulation of medicaments rather than to new and better compounds for photodynamic therapy. Chowdhary et al mentions phenothiazines and at para [0049] provides examples which include ring substituted compounds such as 1,9-dimethyl derivatives. There is nothing in Chowdhary et al that would have motivated a skilled person to put aside the conventional wisdom and to increase the alkyl chain length of the hydrocarbon group on the N atom. Accordingly, nothing in Chowdhary et al would have cured the fundamental failings of Wilson et al, Biel, and Wainwright et al.

In view of the above, reconsideration is requested.

Claims 77-79, 89-91, and 98-100 stand provisionally rejected as allegedly representing obviousness-type double patenting over claims 7 and 8 of Application 11/723,523, in light of the Merck Index, in view of Biel, Wainwright et al and Chowdhary et al. As described in §804 of the U.S. MPEP (pg. 800-15):

> If the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the Examiner should then withdraw that rejection and permit the application to

> issue as a patent, thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Accordingly, Applicants submit that the provisional double patenting rejection should be withdrawn in the present application (i.e., the earlier filed application) as described above once the provisional double patenting rejection in the present application is the only rejection remaining in the present application.

Finally, during the interview, the Examiner's attention was directed to the fact that a compound recited in the presently presented claims is the first (and currently only) new photo-antimicrobial compound tested in a fully randomized clinical trial in human patients (see attached press release). The trial has shown good statistical data for anti-infective properties, and had also demonstrated eradication of MRSA in humans.

The Examiner is requested to consider the documents listed on the attached PTO/SB/08a Form and to initial and return that Form.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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